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EXAMINER	
CHUNDURU, SURYAPRABHA	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 08/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/747,538	KATZ ET AL.	
	Examiner	Art Unit	
	Suryaprabha Chunduru	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,18,38-41 and 43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,18,38-41 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. 7/15/05
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' response to the office action filed on May 24, 2005 has been entered.

2. Claims 17-18, 38-41, and 43 are pending.

Status of the Application

3. Applicants' response to the office action is fully considered and found not persuasive. All arguments have been fully considered and thoroughly reviewed, but are deemed not persuasive for the reasons that follow. This action is made FINAL.

4. The following are the rejections made in the previous office action:

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

A. Claims 17 and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Wittwer et al. (USPN. 6,232,079).

Wittwer et al. teach a method of claim 17, for monitoring hybridization during PCR for detecting a target nucleic acid sequence in a test sample comprising

(a) contacting the test sample with amplification reagents comprising a polymerase, a PCR primer pair, and a probe (see column 6, lines 1-15, column 44, lines 24-38);

(b) performing PCR cycles (i) raising temperature to dissociate the double-stranded genomic DNA, (ii) lowering the temperature to allow primers and probe to hybridize to the target nucleic acid, (iii and iv) raising the temperature to dissociate the target-probe hybrids and extending the primers and continuously raising the temperature to temperature dependent polymerase extension (see column 44, lines 50-67, column 45, lines 1-12 wherein the step of maintaining the reaction mixture for a time and at a temperature sufficient to dissociate the probe hybrid and activating polymerase to a temperature to initiate primer extension occurs simultaneously, see also col.29, line 13-36, col. 35, line 8-31);

(c) repeatedly performing the PCR cycles to form an amplification product (see column 45, lines 13-53) and (d) detection of the amplification product as an indication of presence of the nucleic acid (see column 45, lines 13-53).

With regard to claim 18, Wittwer et al. also disclose that the target nucleic acid sequence is a polymorphic nucleic acid sequence (see column 44, lines 24-38). Thus the disclosure of Wittwer et al. meets the limitations in the instant claims.

B. Claims 38-40, 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Meyer et al. (USPN. 5,648,482).

Meyer teaches a method of claim 38, for determining deletion or insertion (mutant alleles) of at least 50 base pairs in DNA in a test sample comprising:

(a) contacting the test sample with amplification reagents, wherein the amplification reagents comprise amplification primers, to form a reaction mixture in which the amplification primers hybridize with a target nucleic acid sequence (mutant alleles) and a standard nucleic acid sequence (wild-type) in the test sample (see col. 6, line 1-4);

(b) subjecting the reaction mixture to amplification conditions to form a target nucleic acid amplification product, if the target nucleic acid is present in the test sample (mutant allele- short fragment) and a standard nucleic acid amplification product (wild-type – long product) (see col. 6, line 4-14, line 53-67, col. 7, line 1-7, col. 9, line 13-40);

(c, d) detecting first and second signal that is proportional to the amount of the target and standard nucleic acid amplification product (see col. line 6-20, line 65-67, col. 7, line 1-7, col. 9, line Fig. 9, col. 9, line15-29);

(e) comparing the first signal to second signal to determine whether a deletion or insertion of at least 50 base pairs is present in DNA in the test sample, wherein the amplification reagents comprise one primer that hybridizes to both the target and the standard nucleic acid sequence (see col. 9, line 15-35, wherein SEQ ID No.1 hybridizes to both mutant and wild-type nucleic acid sequence).

With regard to claims 39-40, Meyer teaches that the deletion or insertion (mutant allele) comprises base pairs ranging from at least 200 to 1000 bp (see col. 9, line 15-40).

With regard claim 43, Meyer teaches that the deletion or insertion (mutation) is in the CYP2D6 locus (see col. 9, line 15-40).

Thus the disclosure of Meyer meets the limitations in the instant claims.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Meyer (USPN. 5,648,482) in view of Wittwer et al. (USPN. 6,232,079). .

Meyer teaches a method of claim 38, for determining deletion or insertion (mutant alleles) of at least 50 base pairs in DNA in a test sample comprising:

(a) contacting the test sample with amplification reagents, wherein the amplification reagents comprise amplification primers, to form a reaction mixture in which the amplification primers hybridize with a target nucleic acid sequence (mutant alleles) and a standard nucleic acid sequence (wild-type) in the test sample (see col. 6, line 1-4);

(b) subjecting the reaction mixture to amplification conditions to form a target nucleic acid amplification product, if the target nucleic acid is present in the test sample (mutant allele- short

fragment) and a standard nucleic acid amplification product (wild-type – long product) (see col. 6, line 4-14, line 53-67, col. 7, line 1-7, col. 9, line 13-40);

(c, d) detecting first and second signal that is proportional to the amount of the target and standard nucleic acid amplification product (see col. line 6-20, line 65-67, col. 7, line 1-7, col. 9, line Fig. 9, col. 9, line 15-29);

(e) comparing the first signal to second signal to determine whether a deletion or insertion of at least 50 base pairs is present in DNA in the test sample, wherein the amplification reagents comprise one primer that hybridizes to both the target and the standard nucleic acid sequence (see col. 9, line 15-35, wherein SEQ ID No. 1 hybridizes to both mutant and wild-type nucleic acid sequence). However Meyer did not specifically teach amplification in the presence of a probe using probe-target melting temperatures.

Wittwer et al. teach a method for monitoring hybridization during PCR for detecting a target nucleic acid sequence in a test sample comprising (a) contacting the test sample with amplification reagents comprising a polymerase, a PCR primer pair, and a probe (see column 6, lines 1-15, column 44, lines 24-38); (b) performing PCR cycles (i) raising temperature to dissociate the double-stranded genomic DNA, lowering the temperature to allow primers and probe to hybridize to the target nucleic acid, raising the temperature to dissociate the target-probe hybrids and extending the primers and continuously raising the temperature to temperature dependent polymerase extension (see column 44, lines 50-67, column 45, lines 1-12); (c) repeatedly performing the PCR cycles to form an amplification product (see column 45, lines 13-53) and (d) detection of the amplification product as an indication of presence of the nucleic acid (see column 45, lines 13-53).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to combine the method of amplification of a target nucleic acid as taught by Meyer with the step of primer extension in the presence of a probe or monitoring hybridization during PCR as taught by Wittwer et al. to achieve expected advantage of developing a sensitive and enhanced method for amplification of a specific target. An ordinary skill in the art would have reasonable expectation of success that the modification of the method taught by Meyer with the step of monitoring hybridization during PCR would result in continuously monitoring of DNA amplification, identification and quantitation of the target nucleic acid and reducing laborious processing steps after PCR to identify the said target nucleic acid (see col. 3, line 14-33). Therefore an ordinary practitioner would have been motivated to combine the method of Meyer with the inclusion of step of monitoring hybridization during PCR as taught by Wittwer et al. to develop a sensitive and enhanced method for amplification and quantitation of a specific target nucleic acid.

Response to arguments

7. With regard to the rejection made in the previous office action under 35 USC 102(e) over Wittwer et al., Applicants' arguments and amendment have been fully considered and found unpersuasive. Applicants' argue that Wittwer et al. did not teach step (b) of claim 17 reciting four steps using four temperatures within one cycle and argue that the disclosure of Wittwer et al. does not anticipate the instant invention. Applicants' arguments are fully considered and found unpersuasive for two reasons. First, the four temperature cycle of step (b) of claim 17, is braoder in scope and does not exclude the temperature cycle disclosed by Wittwer et al. Second, the disclosure of Wittwer et al. the step of maintaining the reaction mixture for a time and at a

temperature sufficient to dissociate the probe hybrid and activating polymerase to a temperature to initiate primer extension occurring simultaneously and repeatedly cycled to form an amplification product which reads on the step (b) of the instant claim 17. Since the instant claims do not recite any specific temperatures at which the sep (b) is performed, the instant claims red on temperatures as disclosed by Witwer et al. Thus the disclosure of Wittwer et al. does not exclude the steps as claimed in the instant claims. Applicants' further argue that Wittwer et al. teach detection of single base mutations and does not disclose detection of large deletions or insertions. Applicants' arguments are fully considered and found unpersuasive. The amendment reciting " suspected of having single or large deletions or insertions" in the preamble of the claim is not given any patentable weight, because the method steps are anticipated and similar to that disclosed by Wittwer et al. and inherently possesses the function of detecting either single or large deletions or insertions. In addition Applicants agree that Wittwer et al. teaches detection of single mutations, which meets the limitation in the preamble reciting "single or..." . Therefore the disclosure of Wittwer et al. does anticipate the instant claims and the rejection is maintained and rewritten as above.

8. With regard to the rejection under 35 USC 102(b) as anticipated by Meyer et al. , Applicants' arguments are fully considered and found unpersuasive. Applicants argue that Meyer et al. does not teach deletion of at least 50 bases pairs and a primer hybridizing to both the target and standard nucleic sequence. Applicants further argue that Meyer et al. teaches amplification of fragments such as containing 739 bp or 1123 bp and does not teach teach deletion or insertions in these fragments. Applicants' arguments are fully considered and found unpersuasive because Meyer et al. does disclose detection of mutations which comprise deletions or insertions of at

least 50 bp. The fragments amplified indicate that the standard (wild type) nucleic acid sequence is 1123 bp and the mutation comprising fragment is 739 bp, which indicates that the fragment of 739 lacks (deletion) a sequence of (1123 – 739 = 384 bp) which meets the limitation atleast 50 bp deletion. Applicants further argue that Meyer et al. teach two different primers in two separate reactions and therefore does not anticipate the instant claims. Applicants' arguments are fully considered and found unpersuasive because the instant claims recite "contacting the test sample with reaction reagents, wherein the amplification reagents comprise amplification primers (plurality), to form a reaction mixture in which the amplification primers hybridize with a target and a standard nucleic acid sequence" in step (a) of claim 38 and does not recite the limitation of a single primer hybridizing to both target and standard nucleic acid, thus the limitation upon which the arguments are based, is not present in the instant claims. In addition, the claims are in comprising format thus any additional steps are permissive. Thus the disclosure of Meyer reciting contacting the test and control sample with primers in two separate reactions is within the scope of the instant claims. Therefore the rejection is maintained herein.

9. With regard to the rejection under 35 USC 103(a) as being obvious over Meyer et al. in view of Wittwer et al. Applicants' arguments are fully considered and found unpersuasive. Applicants argue that Meyer et al. does not teach or suggest the claimed invention and Wittwer et al. does not remedy the deficiencies of Meyer et al. As discussed above Meyer et al. doest teach the instant claims it is obvious t to combine the method of Meyer et al. with the teachings of Wittwer et al. to achieve the expected advantage of developing an improved method, because examiner notes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or

motivation to do so found either in thereferences themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir.1992). In this case, specific motivation is provided in the rejection, which states that An ordinary skill in the art would have reasonable expectation of success that the modification of the method taught by Meyer with the step of monitoring hybridization during PCR would result in continuously monitoring of DNA amplification, identification and quantitation of the target nucleic acid and reducing laborious processing steps after PCR to identify the said target nucleic acid (see col. 3, line 14-33). Therefore the rejection is maintained herein.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 571-272-0783. The examiner can normally be reached on 8.30A.M. - 4.30P.M, Mon - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and - for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Suryaprabha Chunduru
Patent Examiner
Art Unit 1637
August 2, 2005

JEFFREY FREDMAN
PRIMARY EXAMINER
8/3/05